REMARKS

In the Claims:

The dependency of claims 31 and 32 are amended herein. In particular, claim 31 now depends from claim 27 rather than claim 25. Similarly, claim 32 now depends from claim 27 rather than claim 29.

Priority Determination:

The Examiner contends that the effective priority date for the present application is December 1, 1999, the filing date of PCT/US99/28301. Applicants respectfully disagree.

Claim Rejections:

35 U.S.C. § 102(e)

The Examiner rejects claims 22-27, 31, 33 and 34 under 35 U.S.C. § 102(3) as being anticipated by Holtzman *et al.*, U.S. Patent Application Publication US20020028508, effective filing date, April 23, 1998.

Previously, Applicants relied on *Elan Pharm., Inc. v. Mayo Found. for Med. Ed. & Research* and *Verdegaal Bros. v. Union Oil Co. of California,* and argued that Holtzman *et al.* is not an anticipatory reference because it does not enable the present invention. Additionally, Applicants previously argued that Holtzman *et al.* does not anticipate the present invention because it fails to anticipate each and every element of the presently claimed invention.

In the office action mailed March 17, 2004, the Examiner rejected Applicants' arguments as well as Applicants reliance on *Elan Pharm., Inc. v. Mayo Found. for Med. Ed. & Research* and *Verdegaal Bros. v. Union Oil Co. of California*. Applicants respectfully disagree with the Examiner's analysis and maintain that Holtzman *et al.* is not a proper

anticipatory reference because it does not enable the claimed invention that it is alleged to anticipate and because it does not disclose every element of the claimed invention.

In any event, Applicants additionally submit that Holtzman *et al.* does not anticipate the present invention because Applicants sequenced and isolated the claimed polypeptide prior to the time Holtzman *et al.* was filed. Anticipation under 35 U.S.C. § 102(e) requires that the invention being claimed be "described in (1) an application for a patent, published under section 122(b), by another filed in the United States *before the invention by the applicant for patent.*" (emphasis added). Applicants sequenced and isolated the claimed PRO347 polypeptide before the April 23, 1998 filing date of Holtzman, as is evidenced by the disclosure of the amino acid sequence encoding the PRO347 polypeptide claimed in the present application in U.S. Provisional Application Serial Number 60/069,702, filed 12/16/97. Therefore, Holtzman is not an anticipatory reference under 35 U.S.C. § 102(e).

In support of this argument, Applicants respectfully direct the Examiner's attention to the attached declarations of David Botstein, Audrey Goddard, Paul Godowski, Christopher Grimaldi, Austin Gurney, Margaret Roy, and William Wood under 37 C.F.R. § 1.131.[1] Each of these declarations demonstrates that the nucleic acid and amino acid sequences of the present invention were completed prior to the effective date of the alleged anticipatory reference.

As support for the argument that these declarations overcome the Holtzman reference, the Examiner is first respectfully directed to *In re Stempel*, 113 USPQ 77 (CCPA 1957), where, similar to the present situation, the patent applicant, Stempel, had claims directed to both (i) a particular genus of chemical compounds (the "genus" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. § 102, the examiner cited a prior art reference that disclosed the exact chemical compound recited in

[1] Signed copies of the declarations will be filed in as a Supplementary Amendment as soon as they are received from the inventors.

Stempel's "species" claim. In response to the rejection, Stempel filed a declaration under 37 C.F.R. § 1.131 demonstrating that he possessed that specific chemical compound prior to the effective date of the cited prior art reference. The lower court found the 131 declaration effective to "swear back" of the prior art reference for purposes of allowing a claim to the specific species. However, the lower court relied on the doctrine that prior disclosure of a species is sufficient to anticipate a later claim to a genus encompassing that species to rule the 131 declaration ineffective for swearing behind the cited references for purposes of the "genus" claim.

On appeal, however, the CCPA reversed the decision of the lower court and found Stempel's 131 declaration effective for swearing behind the cited reference for purposes of *both* the "species" claim and the "genus" claim. Specifically, the CCPA stated:

> "We are convinced that under the law all the applicant can be required to show [in a declaration under 37 C.F.R. § 1.131] is priority with respect to **so much of the claimed invention as the reference happens to show.** When he has done this he has disposed of the reference." (*Id.* at 81; emphasis supplied).

Thus, the "Stempel Doctrine" stands for the clear proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he/she made *that portion of the claimed invention* that is disclosed in the prior art reference before the date of the reference. In other words, a patent applicant need not demonstrate that he/she made the entire claimed invention in order to remove a cited prior art reference under 37 C.F.R. § 1.131...to the contrary, he/she only need show prior possession of that portion of the claimed invention that is disclosed in the prior art reference.

The Examiner is also directed respectfully to *In re Clarke*, 148 USPQ 665 (CCPA 1966), which further clarifies the applicability of the Stempel Doctrine to the present situation. Clarke, the patent applicant in *In re Clarke,* filed a patent application claiming a genus of chemical compounds. The reference cited against the Clarke application was a publication showing one species falling within the scope of Clarke's generic claim. In

response, Clarke submitted a declaration under 37 C.F.R. § 1.131 demonstrating that he had conceived of the claimed genus of chemical compounds and actually reduced to practice one species of the genus. However, that species was different from the one disclosed in the cited reference. In other words, Clarke was not able to show that he had actually reduced to practice the same chemical compound that was disclosed in the cited prior art reference. Thus, unlike the patent application in the *In re Stempel* case described above, Clarke did not show complete prior possession of the species disclosed in the cited prior art reference. Nevertheless, the CCPA held Clarke's 131 declaration effective if he showed that reduction to practice of the one species was sufficient to substantiate a claim to the whole genus which included the species disclosed in the reference. The CCPA indicated that such substantiation is provided if the reference species would have been obvious to one of ordinary skill in the art, in light of what the applicant had completed prior to the disclosure of the reference species. Specifically, the CCPA stated:

> "the [Stempel] rule for antedating references is not limited to fact situations where the inventor can show priority to the *identical* compound described in the reference...[a]n applicant should **not** be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the applicant proves was completed with respect to the invention prior to the effective date of the reference...[W]here it can be concluded that facts, offered in a rule 131 affidavit in support of a general allegation of conception and reduction to practice of the invention, would persuade one of ordinary skill in the art to a reasonable certainty that the applicant possessed so much of the invention as to encompass the reference disclosure, then that showing should be accepted as establishing prima facie a case of inventorship prior to the reference. ...Upon satisfying that test, **species of the reference falling within the claim may be antedated indirectly**." (*Id.* at 669-70, emphasis supplied).

Thus, *In re Clarke* clarifies that the Stempel Doctrine described above extends to situations such as the present situation, where the specific sequence disclosed in the allegedly anticipatory reference is not identical to the sequence actually reduced to practice by Applicants.

More specifically, the attached declarations of Botstein *et al.* demonstrate that Applicants isolated and sequenced DNA44176, (SEQ ID NO:49 in the present application), as well as the PRO347 polypeptide, (SEQ ID NO:50 in the present application) (*see* Figure 3 / SEQ ID NO: 3 in U.S. Provisional Application No. 60/069,702) before the filing date of Holtzman *et al.* Holtzman *et al.* disclose an amino acid sequence that is 96.8% identical to SEQ ID NO:50 of the present application. The presently claimed genus encompasses sequences that are at least 95% identical to SEQ ID NO:50. Thus, the amino acid sequence of Holtzman falls within the same genus as Applicants sequence disclosed in U.S. Provisional Application No. 60,069,702, filed 12/16/1997.

As stated in *In re Clarke,* the Stempel Doctrine applies if (1) the compound disclosed in Holtzman *et al.* and the compound reduced to practice by Applicants fall within the same genus and (2) the Holtzman species would have been obvious to one of ordinary skill in the art in light of what Applicants had completed prior to the disclosure of the Holtzman species, *i.e.* Applicants had conceived of the genus prior to Holtzman's disclosure of a species falling within the genus.

As discussed above, the first condition from *In re Clarke* is satisfied in this case. In addition, the declarations of Botstein *et al.,* demonstrate that Applicants had reduced the PRO347 polypeptide to practice and had conceived a genus of variant sequences based on the PRO347 polypeptide sequence before the filing date of Holtzman. In particular, as the inventors attest, they appreciated that the invention of the PRO347 polypeptide included variant sequences at the time they reduced the invention to practice. Numerous passages in U.S. Provisional Application Serial No. 60/069,702 indicate that the inventors conceived of a genus of PRO347 polypeptides. In particular, the passages of the specification quoted in paragraphs 6-8 of the declarations of Wood, Goddard, and Gurney demonstrate this. Specifically, in paragraph 6, the inventors declare that the definition of "native sequence PRO347 polypeptide" found at page 4 of the '702 application includes:

> naturally-occurring truncated or secreted forms of a PRO347 polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of a PRO347 polypeptide.

In addition, at paragraph 7, the inventors declare that at page 7 of the '702 application they explained that the invention included variants:

> In addition to the full-length native sequence PRO347 polypeptide described herein, it is contemplated that PRO347 variants can be prepared. PRO347 variants can be prepared by introducing appropriate nucleotide changes into the PRO347-encoding DNA, or by synthesis of the desired PRO347 polypeptide.

Further, each inventor declares in paragraph 8:

> As one of skill in the art, I appreciated at the time DNA44176 was sequenced, that variations could be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Techniques for achieving sequence variation using site-directed mutagenesis are described in Carter *et al., Nucleic Acids Res.,* 13:4431 (1985) (attached hereto as Exhibit A) and Zoller *et al., Nucleic Acids Res.,* 10:6487 (1982) (attached hereto as Exhibit B). Techniques for achieving sequence variation using cassette mutagenesis are described in Wells *et al., Gene* 34:315 (1985) (attached hereto as Exhibit C). These techniques were described in the '702 application at page 8.

The declarations of Botstein *et al.,* clearly demonstrate that Applicants had conceived a genus of PRO347 sequences by the time the '702 application was filed. Therefore, these declarations fully meet the requirements of both *In re Stempel* and *In re Clarke* and Holtzman *et al.,* has been removed as an anticipatory reference. Applicants respectfully request the rejection be withdrawn.

Additionally, Applicants note that in determining priority for the present application, the Examiner determined that Applicants were not entitled to claim priority to U.S. Provisional Application No. 60/069,702 because the Examiner alleges that application does not provide any utility for the disclosed sequence. Applicants respectfully disagreed with the Examiner's determination. In any event, under the Stempel Doctrine, Applicants may rely on the disclosure of the sequence of SEQ ID NO:50 in U.S. Provisional Application No. 60/069,702 to antedate the Holtzman reference even if the

Examiner maintains that U.S. Provisional Application No. 60/069,702 does not provide a utility for the disclosed sequence.

In particular, the Examiner is respectfully directed to *In re Moore*, 170 USPQ 260 (CCPA 1971), in which the Stempel doctrine was extended to cases where, as in the present case, a reference disclosed a claimed compound but failed to disclose a sufficient utility for it. More specifically, the patent applicant, Moore, claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the examiner cited a reference disclosing the claimed PFDC compound, but not a utility for such compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131, demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had yet to establish a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to effective date of the cited prior art reference, he had not yet completed his "invention."

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relying on the Stempel Doctrine, stated:

> "The determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes." (*Id.* at 267, emphasis supplied).

Thus, *In re Moore* confirms the Stempel Doctrine holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of the claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either with or absent a utility different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that

reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant only needs to demonstrate that he or she had possession of the claimed chemical compound before the effective date of the prior art reference.

As argued in the Amendment and Request for Reconsideration submitted 24 December 2003, Holtzman *et al.* does not disclose either a specific and substantial utility or a well-established utility for the sequence disclosed therein. Thus, Applicants are not required to show a utility to antedate Holtzman, but rather are only required to show prior conception of the genus and sequence presently claimed. Hence, considered in light of the Stempel Doctrine, as extended by *In re Clarke* and *In re Moore,* the declarations of inventors Botstein *et al.* demonstrate that Holtzman *et al.* does not anticipate the presently claimed invention and Applicants respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 102 (a)

The Examiner also rejects claims 22-36 under 35 U.S.C. § 102(a) as being anticipated by Botstein *et al.,* WO/9935170, July 15, 1999 and rejects claims 22-27, 31, 33, and 34 under 35 U.S.C. § 102(a) as being anticipated by Holtzman *et al.,* WO 99/54343, Oct. 28, 1999. Applicants respectfully disagree with these grounds of rejection.

First, Applicants note that although Holtzman *et al.*, WO 99/54343, like Holtzman *et al.,* U.S. Patent Application Publication US20020028508, discloses an amino acid sequence that is 96.8% identical to SEQ ID NO:50, it does not disclose any utility for that amino acid sequence. Specifically, WO 99/54343 does not disclose any working example of a credible, specific and substantial utility for T139. Thus, Applicants respectfully submit that the declarations of Botstein *et al.* overcome WO 99/54343 for the same reasons (discussed above) those declarations overcome Holtzman *et al.,* U.S. Patent Application Publication US20020028508. Applicants respectfully request this ground of rejection be withdrawn.

Second, the declarations of Botstein *et al.* demonstrate that the nucleic acid and amino acid sequences of the present invention were completed prior to the effective date of the Botstein reference (WO 99/35170, filed 7/15/99) currently cited against Applicants. Anticipation under 35 U.S.C. § 102 (a) requires that "the invention was . . . patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." Therefore, Botstein, WO 99/35170, does not anticipate the present invention.

In particular, Applicants respectfully direct the Examiner's attention to paragraph 9 of the Goddard, Gurney, Godowski, and Wood declarations, which state:

> 9. Prior to July 15, 1999, the filing date of WO 99/35170, I conceived and reduced to practice in the United States the nucleic and amino acid sequences encoding PRO347, as demonstrated by their disclosure in U.S. Provisional Application Serial No. 60/113,296 ("the '296 application"), filed 12/22/98. The nucleic acid sequence encoding PRO347 is identified as DNA44176 and is shown in Figure 13 (SEQ ID NO:13) of the '296 application. This sequence corresponds to SEQ ID NO:49 in the '664 application. The amino acid sequence encoding PRO347 is shown in Figure 14 (SEQ ID NO:14) of the '296 application, which corresponds with SEQ ID NO:50 in the '664 application.

The Botstein reference cited by the Examiner, the '296 application referenced in the inventor declarations, and SEQ ID NO:50 of the present application all disclose identical amino acid sequences for PRO347. Additionally, the disclosure of the Botstein reference cited by the Examiner and the disclosure in the '296 application are identical. Thus, consistent with *In re Stemple,* 113 USPQ 77 (CCPA 1957), Applicants have shown they earlier disclosed "so much of the claimed invention as the reference happens to show" and therefore, have overcome the Botstein reference cited by the Examiner. Applicants respectfully request this ground of rejection be withdrawn.

35 U.S.C. § 101 – Utility

Although the Examiner recognizes that the nucleic acid encoding PRO347 is supported by a diagnostic utility for lung and colon cancers (Office Action mailed 9/24/03, p.5), the Examiner rejects the present invention, the PRO347 polypeptide, for lack of utility.

In particular, the Examiner rejects claims 25-34 and 36 under 35 U.S.C. § 101, alleging that the claimed invention is not supported by either a substantial asserted utility or a well established utility. According to the Examiner, in the "absence (of) evidence that the polypeptide is expressed at an elevated level one would conclude that the claimed invention is not supported by either a substantial asserted utility or a well established utility." In particular, the Examiner relies on three references, Pennica *et al.*, Haynes *et al.*, and Gygi *et al.*, as support for the argument that amplified levels of PRO347 DNA do not necessarily correlate to overexpression of the encoded PRO347 polypeptide.

Applicants respectfully disagree that the presently claim invention is not supported by either a substantial asserted utility or a well established utility. First, setting the standard for satisfying the utility requirement too high, the Examiner improperly rejects Applicants' assertions of utility at pages 119 and 137 in the specification. Second, the references relied on by the Examiner, Pennica *et al.*, Haynes *et al.*, and Gygi *et al.*, do not outweigh the evidence Applicants herein submit as support demonstrating that those of skill in the art would reasonably expect the protein expression levels of the claimed polypeptides to correlate to the amplified levels of DNA. Third, consistent with the standards set forth in the *Revised Interim Utility Guidelines Training Materials,* (available at http://www.uspto.gov/ web/offices/ pac/utility/utilityguide.pdf), the present invention is supported by a specific, substantial, and credible utility.

1. The Examiner Sets the Utility Bar Too High

At pages 119 and 137 of the specification Applicants assert a specific, substantial, and credible utility for the claimed invention:

> PRO 327-, PRO344-, PRO347-, PRO357-, and PRO715-encoding genes are amplified in the genome of certain lung, colon, and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. Therapeutic agents may take the form of antagonists of PRO327, PRO344, PRO347, PRO357 aor (sic) PRO715 polypeptide, for example, murine-human chimeric, humanized or human antibodies against a PRO327, PRO344,

> PRO347, PRO357, or PRO715 polypeptide. These amplifications are useful as diagnostic markers for the presence of a specific type of tumor.

(p.119)

> The polypeptides encoded by the DNAs tested have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples.

(p.137)

An Applicant's assertion of utility creates a presumption of utility sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 183 USPQ 288, 297 (CCPA 1974). *See also In re Jolles*, 206 USPQ 885 (CCPA 1980); *In re Irons*, 144 USPQ 351 (9165); *In re Sichert*, 196 USPQ 209, 212-213 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Further, statistical certainty regarding Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler,* 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Where an Applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Significantly, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added).

Consideration of the totality of the evidence discussed below clearly demonstrates that the proposition that there will be correlation between protein and transcript levels does not violate scientific principles nor is it wholly inconsistent with knowledge in the art. Thus, the maintained rejection of the present claims for lack of utility is improper and should be withdrawn.

a) It is a general scientific principle that DNA is transcribed into RNA which is translated into protein.

According to Genes V, a central dogma of molecular biology is that genes are perpetuated as nucleic acid sequences, but function by being expressed in the form of proteins. Thus, genetic information is perpetuated by replication where a double-stranded nucleic acid is duplicated to give identical copies. These copies are then expressed by a two-stage process. First, transcription generates a single-stranded RNA identical in sequence with one of the strands of the duplex DNA. This RNA strand is then translated such that the nucleotide sequence of the RNA is converted into the sequence of amino acids comprising a protein. *See* Lewin, Bejamin. *Genes V.* 1994. Oxford University Press, NY, NY. p. 163.

Thus, those of skill in the art generally accept that gene expression levels correlate to protein expression levels absent specific events such as translation regulation, post-translation processing, protein degradation, protein isolating errors, etc. *See* Orntoft *et al.,* "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45. Therefore, Applicants' assertion that the claimed polypeptides are supported by a diagnostic utility because they are encoded by nucleic acids that are amplified in lung and colon tumors does not violate scientific principles.

b) Utility of the Claimed Polypeptides is Not Inconsistent with Knowledge in the Art

Pollack, Orntoft, Hyman, Bermont, Varis, and Hu demonstrate that the utility of the claimed polypeptides is not wholly inconsistent with the knowledge in the art. These references further support Applicants' argument that one of ordinary skill in the art

would reasonably conclude that the present invention is supported by a specific, substantial, and credible utility.

For example, Pollack *et al.* profiled DNA copy number alterations across 6,691 mapped human genes in 44 breast tumors and 10 breast cancer cell lines and reported that microarray measurements of mRNA levels revealed remarkable degrees to which variation in gene copy number contributes to variation in gene expression in tumor cells. *See* Pollack *et al.,* "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS,* 99(20):12963-12968. Pollack *et al* further report that their findings that DNA copy number plays a role in gene expression levels are generalizable. Thus significantly, "[t]hese findings provide evidence that widespread DNA copy number alteration can lead directly to global deregulation of gene expression, which may contribute to the development or progression of cancer."

In particular, Pollack *et al.* report a parallel analysis of DNA copy number and mRNA levels. Pollack *et al.* found that "[t]he overall patterns of gene amplification and elevated gene expression are *quite concordant, i.e.*, a significant fraction of highly amplified genes appear to be correspondingly highly expressed." (emphasis added). Specifically, of 117 high-level DNA amplifications 62% were associated with at least moderately elevated mRNA levels and 42% were found associated with comparably highly elevated mRNA levels.

Orntoft *et al.* report similar findings in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45. Initially, Orntoft *et al.* note that "[h]igh throughput array studies of the breast cancer cell line BT474 ha(ve) suggested that there is a correlation between DNA copy numbers and gene expression in highly amplified areas ( ), and studies of individual genes in solid tumors have revealed a good correlation between gene dose and mRNA or protein levels in the case of c-erb-B2, *cyclin d1, ems1,* and N-myc." Orntoft *et al.,* at p. 37.

Specifically, Orntoft *et al.* used 2D-PAGE analysis on four breast tumor tissue samples to determine correlation between genomic and protein expression levels of 40 well resolved, known proteins. Orntoft reported that "[i[n general there was a *highly significant correlation* ($p<0.005$) between mRNA and protein alterations ( ). Only one gene showed disagreement between transcript alteration and protein alteration." (emphasis added). Orntoft *et al.,* at p. 42. Additionally, Orntoft *et al.* report that "11 chromosomal regions where CGH showed aberrations that corresponded to the changes in transcript levels also showed corresponding changes in the protein level ( )." Orntoft *et al.,* at p. 43. The regions examined by Orntoft include genes encoding proteins that are often found altered in bladder cancer.

Orntoft *et al.* note that their study reports a *striking correspondence* between DNA copy number, mRNA expression and protein expression. Orntoft *et al.*, further note that any observed discrepancies in correlation may be attributed to translation regulation, post-translation processing, protein degradation or some combination of these. *See also* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research*, 62:62-40-6245.

Varis and Bermont are yet further examples that utility of the present invention based on a correlation between gene amplification and protein overexpression is not wholly inconsistent with knowledge in the art. Varis *et al.*, carried out a comprehensive analysis of gene copy number and expression levels of 636 chromosome 17-specific genes in gastric cancer. *See* Varis *et al.*, "Targets of gene amplification and overexpression at 17q in gastric cancer." *Cancer Res.* 2002. 1;62(9):2625-9. Specifically, Varis *et al.* report that analysis of DNA copy number changes by comparative genomic hybridization on a cDNA microarray revealed increased copy numbers of 11 genes, 8 of which were found to be overexpressed in the expression analysis. Thus, Varis *et al.*, teach there is a 72% correlation between increased DNA copy number and gene expression level.

Bermont teaches that overexpression of p185 is usually associated with c-erbB-2 amplification. Specifically, Bermont reports that 100% of the overexpressed p185

protein in 106 breast cancer samples studied also displayed c-erbB-2 amplification. *See* Bermont *et al.*, "Relevance of p185 HER-2/neu oncoprotein quantification in human primary breast carcinoma." *Breast Cancer Res Treat.* 2000 63(2):163-9. *See also* Hu *et al.*, "Profiling of differentially expressed cancer-related genes in esophageal squamous cell carcinoma (ESCC) using human cancer cDNA arrays: overexpression of oncogene MET correlates with tumor differentiation in ESCC." *Clin Cancer Res.* 2001 7(11):3519-25 (the results of cDNA arrays showed that 13 cancer-related genes were upregulated > or = 2 fold and immunostaining results of the expression of the MET gene showed MET overexpression at the protein level, validating the cDNA arrays findings).

Thus, although there may not always be a 100% correlation between gene amplification and protein overexpression, the above discussed references evidence that the utility of the present invention is not wholly inconsistent with the knowledge in the art, and therefore, also evidence that one of ordinary skill in the art would believe that the claimed invention is supported by a specific, substantial, and credible utility.

2. The References Relied On By The Examiner Do Not Outweigh The Combination Of The Teachings of The Specification, The References Cited by Applicants, And The Expert Declarations Demonstrating Utility

The Examiner argues that:

> [t]he Pennica *et al.* paper provides evidence that there is no positive correlation between DNA amplification and mRNA expression or protein expression. The paper of Haynes *et al.* is evidence that there is not a positive correlation between transcript abundance and protein expression. An additional reference that further supports this is the paper of Gygi *et al.* . . . which expands the work of Haynes *et al.* and provides a more thorough analysis of the data.

Applicants respectfully disagree with the Examiner's analysis of these references.

a) Pennica Teaches A General Correlation Between Gene Amplification And mRNA Levels

Pennica *et al.* recognize that "amplification of protooncogenes is seen in many human tumors and has etiological and prognostic significance." Pennica *et al.*, "WISP genes

are members of the connective tissue growth factor family that are up-regulated in Wnt-1 transformed cells and aberrantly expressed in human colon tumors," *PNAS*. 1998. 95:14717-14722. For this reason, Pennica *et al.* analyzed relative gene amplification and RNA expression of *WISPs-1,2,* and *3* in cell lines, colorectal tumors, and normal mucosa using quantitative PCR.

Initially, Pennica *et al.* noted that *WISPs-1* and *2* had copy numbers that were significantly higher than one, indicating gene amplification. Pennica *et al.* further noted that the copy number for *WISP-3* was indistinguishable from one, indicating no or minimal gene amplification. Pennica *et al.,* at 14720.

Next, Pennica *et al.* examined the levels of *WISP* transcripts in RNA isolated from 19 adenocarcinomas and their matched normal mucosa using quantitative PCR. Pennica *et al* found that *WISP-1* RNA levels displayed good correlation to gene amplification of *WISP-1*. Specifically, Pennica *et al.* found that RNA levels of *WISP-1* in tumor tissue were significantly increased in 84% (16/19) of the human colon tumors examined when compared with normal adjacent mucosa. *See* Pennica *et al.,* at 14721, Figure 7.

However, Pennica *et al.* also found that *WISP-3* RNA levels did not significantly correlate with *WISP-3* gene amplification. In particular, although *WISP-3* did not display significant gene amplification levels, RNA levels in tumor tissue were overexpressed in 63% (12/19) of the human colon tumors examined when compared with normal adjacent mucosa. *See* Pennica *et al.,* at 14721.

Further, as the Examiner notes, Pennica *et al.* also report that *WISP-2* gene amplification levels are negatively correlated with RNA expression levels. That is, although *WISP-2* was significantly amplified, RNA levels of *WISP-2* in tumor tissues were significantly lower than RNA levels of *WISP-2* in normal adjacent mucosa. Specifically, 79% (15/19) of the samples examined displayed this expression pattern. *See* Pennica *et al.,* at 14721.

The Examiner relies on these results as support for the proposition that one of ordinary skill in the art would not expect gene amplification levels to correlate with protein overexpression. Applicants respectfully disagree.

First, *WISP-1* gene amplification and RNA expression levels showed a significant positive correlation. Second, although *WISP-3* was not significantly amplified, it was amplified (*P*=1.666) and significantly overexpressed. Third, although *WISP-2* gene amplification and RNA expression levels seemed to be inversely related, Pennica *et al.* state that this result might be inaccurate. Specifically, Pennica *et al.* suggest that "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." *See* Pennica *et al.,* at 14722. Thus, because the RNA expression pattern of *WISP-2* cannot be accurately attributed to gene amplification of *WISP-2,* this result should be disregarded. Therefore, Pennica *et al.* does not teach that the present invention is not supported by a specific, substantial, and credible utility. Rather, Pennica *et al.,* supports a utility for the present invention because Pennica *et al.* teaches that gene amplification of *WISP-1* strongly correlates (84%) with RNA overexpression.

b) Haynes And Gygi Teach There Is Good Correlation Between Gene And Protein Expression Levels For Amplified Genes

The Examiner also relies on Haynes and Gygi for the proposition that abundance of mRNA expression levels does not necessarily result in increased protein expression levels. Haynes and Gygi are related references based on results obtained from "the mRNA and protein levels of a group of genes expressed in exponentially growing cells of the yeast *S. cerevisiae.*" *See* Haynes, *et al.,* "Proteome analysis: Biological assay or data archive?" *Electrophoresis,* 1998. 19:1862-1871; Gygi *et al.,* "Correlation between Protein and mRNA Abundance in Yeast," *Molecular and Cellular Biology.* 1999. 19(3): 1720-1730. Specifically, Haynes and Gygi "explore a quantitative comparison of mRNA transcript and protein levels for a relatively large number of (yeast) genes expressed in the same metabolic state." *See* Gygi *et al.,* at 1720; Haynes *et al.,* at 1863.

As an initial matter, the results of Haynes and Gygi are not relevant here because they were not obtained in a human system, did not examine any particular human gene or protein expression, and most significantly, did not examine any genes that are amplified in a cancerous state. Instead, Haynes and Gygi both examine the ability to predict protein expression levels in a *biological system.* Specifically, Haynes and Gygi examine whether there is an overall *system* correlation between gene and protein expression levels. *See* Haynes *et al.,* at 1863; Gygi *et al.,* at 1720.

In contrast, the present invention involves the correlation between expression levels of a single gene, the PRO347 nucleic acid, and its encoded polypeptide. PRO347 nucleic acid is amplified in a diseased system, lung and colon tumors.

In any event, even if Haynes and Gygi were a comparable system, both report that "[f]or the entire group (106 genes) for which a complete data set was generated, there was a *general trend of increased protein levels resulting from increased mRNA levels."* Gygi *et al.,* at 1726 (emphasis added); Haynes *et al.,* 1863. In fact, Gygi reports that the Pearson product moment correlation coefficient for the whole data set was 0.935. Gygi *et al.,* at 1726.

The Examiner ignores the overall correlation pattern, which supports the utility of the present invention, and seizes upon a subset of genes studied in Gygi. The Examiner notes that Gygi reports that this subset of genes has only a 0.356 Pearson product moment correlation coefficient.

However, even if the general correlation taught by Haynes and Gygi is rejected, Applicants disagree that the data based on the "subset of genes" the Examiner focuses on teach one of ordinary skill in the art that the present invention is not supported by a utility. Specifically, Gygi *et al.,* separate the genes studied into two groups: (1) those with a message level below 10 copies / cell in a healthy system and (2) those with more than 10 copies for cell. The Examiner's rejection focuses on the first group of genes, but the second group is more relevant to the present invention, which is directed to a polypeptide encoded by an amplified nucleic acid. Indeed, this second group of genes

Gygi *et al.,* studied demonstrated a high correlation between the high message levels of those genes and high protein expression levels. *See* Gygi, *et al.,* at 1726, 1727 (Figure 6). Thus, the Examiner's focus on the first set of genes should be disregarded.

The Examiner's focus on the first set of genes additionally should be disregarded because Gygi *et al.,* note that due to lower message levels, "the error associated with these values (correlation between message and protein levels) may be quite large." Gygi at 1728.

Thus, neither Haynes nor Gygi support the Examiner's rejection of claims 25-34 and 36. Rather, Haynes and Gygi teach there is a good correlation between message and protein levels for genes with high copy numbers per cell, which supports the asserted utility of the present invention.

3. The Claimed Invention is Supported by a Utility that is Specific, Substantial, and Credible

Finally, use of the polypeptide sequence of PRO357 as a diagnostic marker is a specific, substantial and credible utility.

"Specific utility" is defined as:

> [a] utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a polynucleotide whose use is disclosed simply as a 'gene probe' or 'chromosome marker' would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

Revised Interim Utility Guidelines Training Materials, pgs. 5-6 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). The presently claimed polypeptides are asserted to be useful as targets for therapeutic intervention in lung or colon cancer or as diagnostic markers, indicating the presence of tumor cells in lung or colon tissue samples. These utilities are specific to the claimed polypeptides, which are encoded by nucleic acids that are amplified in lung or colon tumors.

"Substantial utility" is defined as:

> a utility that defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measure or further monitoring.

Revised Interim Utility Guidelines Training Materials, pg. 6 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). The presently claimed polypeptides are also supported by a substantial utility because the utilities discussed above, *i.e.* therapeutic targets and diagnostic markers, are real world uses. For example, similar to the statement found in the above quote from the Guidelines, the present specification discloses an assay that measures gene amplification in cancerous cells. The articles discussed above, *supra* at 16-19, correlate that gene amplification in cancerous cells with polypeptide overexpression in cancerous cells. Therefore, the claimed polypeptides are supported by a substantial utility.

"Credible" utility is defined as:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong'. Rather, Office personnel must determine if the assertion of utility is credible (*i.e.,* whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers.

> Therefore the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests.

Revised Interim Utility Guidelines Training Materials, pg. 5 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). The present invention is supported by a credible utility. As discussed above, *supra* at 16-19, the references cited by Applicants demonstrate that the logic underlying Applicants assertion of utility is not seriously flawed, nor are the facts upon which utility is asserted inconsistent with the logic underlying the assertion of utility. Therefore, utilizing the claimed polypeptides as therapeutic targets or diagnostic markers in lung or colon cancer is a credible utility.

A "well established" utility is a:

> specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art.

Revised Interim Utility Guidelines Training Materials, pg. 7 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). For all the above reasons, Applicants have demonstrated currently pending claims 25-34 and 36 are supported by an asserted substantial, specific, and well-established utility and therefore, respectfully request that the rejection of claims 25-34 for lack of utility be withdrawn.

35 U.S.C. § 112, first paragraph - Enablement

In the Final Office Action mailed March 17, 2004 and the Advisory Action mailed October 18, 2004, the Examiner maintains the rejection of Claims 25-34 and 36 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention despite Applicants demonstration that the enablement requirement is satisfied.

1. Applicants Have Enabled Skilled Artisans To Use The Claimed Polypeptides

The Examiner alleges that "since the claimed invention is not supported by either a specific and substantial utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention."

Applicants respectfully disagree. In particular, as discussed above, *supra* at pages 13-25, the claimed polypeptides are supported by the specific, substantial, and credible utility of being therapeutic targets or diagnostic markers in lung or colon tumor tissues. Thus, Applicants respectfully submit that this ground of rejection has been overcome.

2. Pollack, Orntoft, Hyman, Bermont, Varis, and Hu Correlate Gene Amplification And Overexpression Of The Gene Product

Additionally, in rejecting the claims for lack of enablement, the Examiner notes that Applicants have asserted that gene amplification is associated with overexpression of the gene product, but argues that Applicants have not cited any references in support of this statement. Applicants discuss above, *supra* at p. 16-19, several references that support Applicants' statement.

3. The Specification's Disclosure Enables Skilled Artisans Commensurate With The Scope Of The Claims

Yet, according to the Examiner, "[e]ven if the specification were enabling of how to use the PRO347 polypeptide, enablement would not be found commensurate in scope with the claims." In particular, the Examiner argues that one of ordinary skill in the art would not know how to use "variants of 80-99% identity or conservative amino acid substitutions or amino acid additions, deletions, or substitutions."

Applicants respectfully disagree. First, Applicants note that this rejection does not apply to any of claims 27-30 and 32, which are not directed to any variants or to any sequences with substitutions, additions, or deletions.

Second, Applicants note that each of claims 25, 26, 31, 33, and 34 require that the claimed polypeptide have the characteristic of being encoded by a nucleic acid that is

amplified in lung or colon tumors. Thus, one of ordinary skill in the art would be enabled to use the invention of these claims as a therapeutic target or diagnostic marker as discussed above, *supra* at p. 14-15

Third, Applicants have enabled the claimed invention commensurate with the scope of the present claims. In particular, according to MPEP § 2164.01(b), "as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." Applicants disclose at least one method for making and using the claimed invention.

Specifically, from pages 119-137 Applicants disclose the assay and methods used to identify and isolate the PRO347 nucleic acid, which encodes the PRO347 polypeptide claimed in claims 27-31 and 32. Applicants also disclose how to make the variant sequences of claims 25, 26, 31, 33, 34 and 36, at page 59, lines 24-27 of the specification, stating that:

> [g]uidance in determining which amino acid residues may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of known homologous protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology.

Applicants disclose at pages 5, 12-13, and 103 of the specification that portions of the amino acid sequence of the full-length of PRO347 possess significant homology to the cysteine-rich secretory protein-3. Therefore, one of ordinary skill in the art, reading the disclosure, would know to compare the claimed polypeptide sequence with the sequence for the cysteine-rich secretory protein-3 and minimize amino acid changes in regions of high homology between the sequences. Even though the cysteine-rich secretory protein-3 might not be encoded by a nucleic acid that is amplified in lung or colon tumors, it is still a protein with a specific structure. Those of skill in the art will appreciate that those portions of PRO347 possessing significant homology with the cysteine-rich secretory protein-3 likely encode structural features of PRO347.

Therefore, it would be preferred to not introduce sequence alterations in the region encoding structure.

Additionally, the gene amplification assay that Applicants utilized for identifying and isolating the PRO347 nucleic acid and polypeptide, disclosed at pages 119-137 of the specification, can be used to test the ability of any variant sequence to encode a nucleic acid that is amplified in lung or colon tumors. Specifically, at pages 122-137, Applicants disclose an assay for identifying and isolating the nucleic acids of the claimed invention. At pages 120-124 of the specification, Applicants teach that SEQ ID NO:49, which encodes SEQ ID NO:50, may be isolated from lung or colon tumors.

At pages 23-29, and at Table 1, pages 34-54, the specification teaches one of ordinary skill in the art how to determine whether a particular sequence is 95-99% identical to a sequence such as SEQ ID NO: 49. Pages 124-137 of the specification teach one of skill in the art a method for assaying to determine whether a particular sequence has the characteristic of being amplified in lung or colon tumors.

Thus, Applicants have disclosed methods for making and using the claimed invention that bear a reasonable correlation to the scope of the claims and the enablement requirement of 35 U.S.C. § 112 is satisfied. This ground of rejection is overcome and should be withdrawn.

35 U.S.C. § 112, first paragraph - Written Description

Claims 25-34 and 36 are rejected for lack of written description because according to the Examiner, the description in the specification does not convey to those skilled in the art that at the time the application was filed, Applicants were in possession of the claimed invention. Specifically, the Examiner argues the written description requirement is not satisfied because "[t]he specification has disclosed a singled polypeptide, and there is no recited biological function for the protein."

Applicants respectfully disagree. First, Applicants respectfully note that "[a]pplication of the written description requirement ( ) is not subsumed by the 'possession' inquiry."

Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 961, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). Rather, according to MPEP § 2163.02:

> "possession" of an invention may be shown in many ways, only one of which requires actual physical possession or reduction to practice of the claimed invention. For example, "possession" may be shown by "showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 US 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of Calif. v. Eli Lilly,* 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by 'whatever characteristics sufficiently distinguish it').

Additionally, according to MPEP § 2163 (i)(C)(2):

> Whether a specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Applicants have satisfied the written description requirement because they have disclosed a combination of identifying characteristics sufficient to distinguish the claimed invention from other materials. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). Specifically, Applicants have disclosed structure, physical and/or chemical properties, functional characteristics and a method of making the claimed invention.

1. Applicants Have Disclosed A Combination Of Identifying Characteristics Relevant To The Claimed Invention

First, relevant to all pending claims (25-34 and 36), Applicants have disclosed structure by disclosing the nucleic and amino acid sequences of PRO347, SEQ ID NOS: 49 and 50. Further, those of skill in the art, reading the specification would appreciate that the invention of SEQ ID NO:50 was not limited to only this sequence, but that the inventors contemplated and described a genus of sequences with at least 95% sequence identity to SEQ ID NO:50. For example, at pages 60-61 of the specification, Applicants disclose methods of making substitutions, as well as substitutions themselves, which could be used to obtain an amino acid sequence variant of the claimed invention, that is one that shares at least 95% sequence identity with SEQ ID NO:50 and that maintains the characteristic of being amplified in lung or colon tumors. Currently rejected claims 25, 26, 31, 33, 34, and 36 are directed to polypeptides such as these.

Also relevant to all pending claims, in addition to describing the structure of the sequence of SEQ ID NO:50, at page 103, lines 1-29 of the specification, Applicants disclose physical and chemical features of SEQ ID NO: 50, which are common to amino acids that share at least 95% sequence identity with SEQ ID NO: 50. In addition, Figure 20 discloses further features of the encoded polypeptide, which are common to all polypeptides encoded by the claimed genus. For example, polypeptides within the claimed genus have a signal sequence, a transmembrane domain, N-glycosylation sites, a cAMP – and cGMP-dependent protein kinase phosphorylation site, N-myristoylation sites, a prokaryotic membrane lipoprotein lipid attachment site, an EGF-like domain cysteine pattern signature, and C-type lectin domain signature.

Each of claims 25, 26, 31, 33, 34, and 36 require that the claimed polypeptide variants have the characteristic of being encoded by a nucleic acid that is amplified in lung or colon tumors. The Examiner disagrees that being "encoded by a nucleic acid that is amplified in lung or colon tumors" is a biological activity of the claimed polypeptide. However, "biological activity" is not the proper standard. As discussed above, a claim to a genus may be adequately described by description of *characteristics* that are common to the genus and allow those of skill in the art to determine whether a particular species

falls within the scope of the genus. MPEP § 2163. Being "encoded by a nucleic acid that is amplified in lung or colon tumors" is one characteristic which distinguishes members of the claimed genus from other polypeptides.

In addition to describing structure, physical and chemical properties and characteristics of the polypeptides claimed in claims 25-34 and 36, Applicants also have disclosed how to "make" the claimed invention as discussed above. *See supra* at p. 27-28.

Thus, based on the above combination of described factors, Applicants have demonstrated possession of the claimed invention and provided an adequate written description of the invention. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

2. Applicants' Specification Complies With Example 13 In The Training Materials

Additionally, Applicants maintain that the claimed invention satisfies the written description requirement under the analysis of Example 13 of the Training Materials which accompany the Written Description Guidelines. Specifically, according to Example 13, a claim to "[a]n isolated variant of the protein of claim 1" is not adequately described if: (1) the specification and claim do not indicate what distinguishing attributes are shard by members of the claimed genus; (2) the specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or addition; and (3) the specification and claim fail to disclose structural features that could distinguish compounds in the genus from those outside the genus.

Claims 25, 26, 31, 33, and 34 are adequately described under this analysis because, as discussed above, the specification and the claim do indicate distinguishing attributes that are shared by members of the claimed genus; for example being encoded by a nucleic acid that is amplified in lung or colon tumors. Additionally, the claims limit the number of substitutions, deletions, insertions, and/or additions by requiring all sequences within the genus to have at least 95% sequence identity to SEQ ID NO:50. Finally, the present specification at page 103 and Figure 20 discloses several structural

features common to species falling within the claimed genus. Hence, Example 13 further evidences that the present invention is adequately described.

The Examiner rejects Applicants' reliance on Example 13 of the Training Materials, alleging that the distinguishing attribute of being encoded by a nucleic acid that is amplified in lung or colon tumors is an attribute of the nucleic acid, not the protein. (Advisory Action mailed October 18, 2004).

Applicants respectfully disagree. Being *encoded* by a nucleic acid that is amplified in lung and colon tumors is a characteristic of the claimed polypeptides. Further, as discussed above, the claimed polypeptides have the additional characteristic of being overexpressed in lung and colon tumor tissues.

For all of the reasons discussed above, Applicants have satisfied the written description requirement of 35 U.S.C § 112, 1 and respectfully request this ground of rejection be withdrawn.

SUMMARY

Applicants believe that currently pending Claims 25-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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